



Human Germline Editing: Science or Fiction?

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Overview



“They’re going to CRISPR people. What could possibly go wrong?”

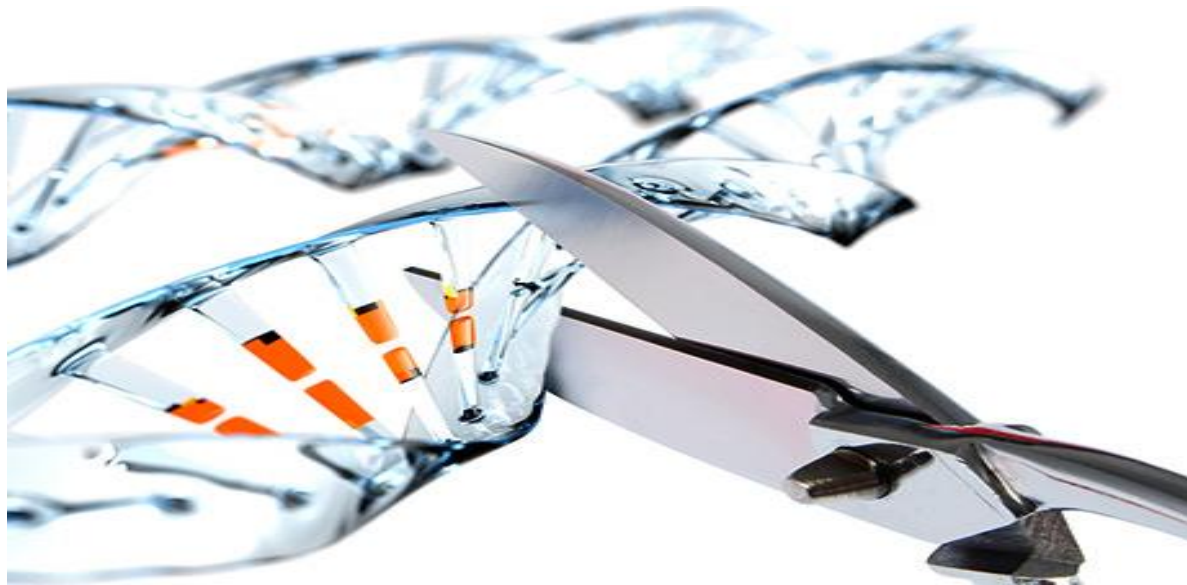
- headline from June 2016 article in STAT by science writer Sharon Begley
- cautions are both principled & practical
- mosaicism
- off-target mutations
- monitoring the genome
- born a subject/subject for life
- IVF & PGD: current practices
- the lab vs. the world:
 - news, funding, rewards
- the unavoidable policy problem:
 - where do our efforts belong?
 - what do we owe each other and why?

It's Not All About Genes

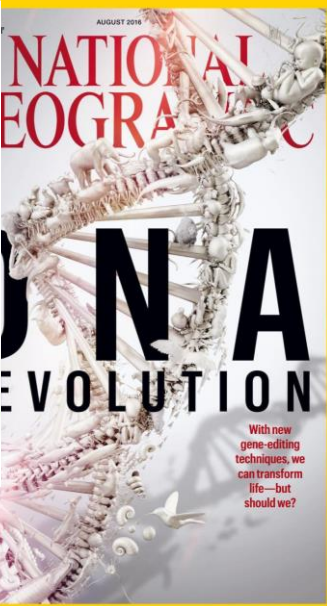
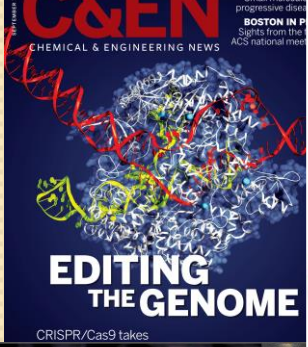
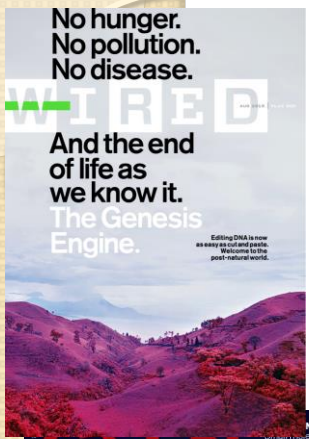
- Individual health and personal characteristics are also significantly influenced by: epigenetics, other environmental factors, nurture, the microbiome, life experiences, socioeconomic status, “social capital,” where you live, where you work, who you know, and many more imperfectly understood factors
- But in contemporary academia, Genes R Us
 - Belsky et al., “Genetic Analysis of Social-Class Mobility in Five Longitudinal Studies,” PNAS 2018;115:E7275-E7284 <https://doi.org/10.1073/pnas.1801238115>

Somatic Cell Genome Editing

- Zinc finger nucleases, TALENs, and other genome editing techniques have been in use for decades
- CRISPR-Cas9 made news because it is easy



CRISPR-Cas9 in the News



Limits of Somatic Cell Genome Editing

- Specific, targeted edits can work in adults and children
 - Example: deleting APOE gene variant linked to cardiovascular disease and Alzheimer's disease
 - Risk: do we know everything that every genetic variant does? could we delete something useful?
- Ex vivo edits to hematopoietic stem cells may work best
 - Example: sickle cell disease
- Many genetic diseases with systemic effects probably can't be treated effectively that way
 - Example: first in vivo editing trial (using ZFNs) began last November for (most manifestations of) Hunter syndrome
- New: 80+ patient-subjects have apparently received somatic cell gene editing in China to date (## & regulatory oversight are unclear)
- Newer: RNA editing and base editing may be more versatile, accurate, and precise

Editing Embryos, Zygotes, Gametes

- **Non-viable human embryos edited in China (2015)**
 - Results were lousy: extensive mosaicism, many “off-target” mutations
 - Requires IVF, then PGD to check safety & efficacy
- **OHSU’s Mitalipov edited zygotes (summer 2017)**
 - Claimed high success rate, little mosaicism, few off-target effects
 - Requires IVF, then PGD to check safety & efficacy
 - Questioned claim: that maternal DNA was preferentially inserted
- **Gamete editing: more accurate?**
 - Still requires testing (IVF&PGD, or equivalent) to check safety & efficacy
- **Long-term follow-up needed!**
- **Germline elimination of genetic disease is easier with IVF&PGD alone, to select unaffected embryos**
 - Very few instances where this cannot work
 - Alternatives exist; all require knowledge of at-risk status
- **Ideal Editing Result: targeted, accurate, precise, inheritable changes**
- **Big Question: Is that the goal, or just the means of effective correction?**

Germline Genome Editing: Needed or Wanted?

- If germline effects are the goal, not merely a “lucky” side effect of effective treatment:
 - IVF&PGD can address nearly all instances except dominant & homozygous mutations
- Should we want to edit the inheritable human genome?
 - Is it different from the effects of selective reproduction (using IVF&PGD, or not having genetically related children)?
- Can multiple individual corrective choices add up to alteration of the global human genetic inheritance?
 - Probably not; but do individual choices reflect (or contribute to) “social desirability eugenics”? Think GATTACA

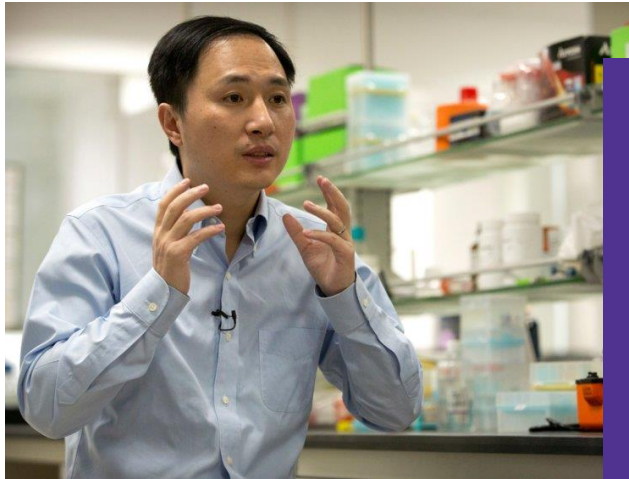
Is Germline Editing Good Science?

- Is it the best available way to correct genetic disease?
- If mutations are known:
 - IVF/PGD can address nearly all instances
 - Exceptions: dominant & homozygous mutations
- But many disorders are complex and multigenic
 - Both disease susceptibility and familial similarities are also governed by: epigenetics, other environmental factors, nurture, the microbiome, life experiences, SES, where you live, where you work, and many more poorly understood factors
- Prioritizing genetic relationships: are there consequences?
 - We are all closely related already
- What makes you you?

Why Rush to Clinical Application?

- IVF & PGD & cool technology > IVF & PGD
 - otherwise, we would have been talking long ago about making ART more broadly accessible
- Technophilia urges us to expand “need” – here as for other need expansions
- Insufficient Reason #1: not enough embryos
 - # of embryos implanted should be limited; # of implantation attempts is limited by many factors
- Insufficient Reason #2: correcting the same potential person
 - “I’m using ART but making only one zygote for religious reasons” is philosophically interesting but implausible in real-world ethics

And Then Came the CRISPR Babies



Place Your
CRISPR
Order

Order Now



Moratorium vs. Desire

- Critiques of He Jiankui's ethics
- Critiques of He Jiankui's process
- Calls for a moratorium on clinical applications
- Requests for help with clinical applications
- At least one announcement of intent to edit more embryos
- Fame, notoriety, exploitation, & science

Genetic Enhancement: Positional or Intrinsic Good?



Needs, Wants & Enhancing Edits

- Perfecting genome editing enables inheritable “enhancement”
- Are individual enhancing choices different from eliminating disease-causing mutations? That is, can we distinguish “enhancement” from “treatment”? (Or from “prevention”?)
 - Probably not; the distinction is context-dependent
- How can harms and benefits be assessed and balanced in enhancement?
- Can we distinguish enhancements that are positional goods from those that are intrinsic goods?
 - Probably not, when the context keeps changing
 - Examples: tolerance for heat, drought, or famine

What Might Drive “Enhancing” Edits?

- How might humans be changed to fit a changing society? Or a changing planet?
- Could thinking this way turn us away from other ways of addressing adverse social and environmental influences?
- Other ways include learning more about many poorly understood, intersectional, and hard-to-address factors
 - Examples: epigenetics, other environmental factors, nurture, the microbiome, life experiences, SES, where you live, where you work, etc.
- HIV susceptibility can be minimized in many ways

Justice Implications

- Could focusing on genome editing:
 - increase \$-related health disparities?
 - turn us away from non-genetic ways to reduce health disparities?
- Should this be solved by making genome editing – or even just IVF&PGD – available to all?
- Or are we simply too in love with science?
 - as long as we believe it to be quick, clean, and easier than social progress
- Continued attention to epigenetics, other environmental factors, nurture, the microbiome, life experiences, SES, where you live, where you work, etc. is essential to justice in science & society

Global Governance & Oversight

- NexTRAC: domestic oversight?
- “soft law” governance coordination?
- WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing
- International Commission on the Clinical Use of Human Germline Genome Editing
 - NAM, NAS, UK Royal Society
- Clinical applications of genome editing will almost certainly be difficult to regulate effectively
 - Line-drawing is inevitably somewhat arbitrary
 - IVF & PGD: still essential, still largely unregulated

But Isn't This Still Fiction?

- Yes, but for how long?
 - Impatience as autonomy
- Imperfect & incomplete edits are likely
 - How will we know?
- Global governance is only a bully pulpit
 - --Which could be enough, if we listen to each other
- Patience makes real progress
 - After many years, gene addition & stem cell-based interventions are slowly bearing fruit today
- We still must work to avoid path preclusion & consider the meaning of “need”

OK, Then What?

- Distinguishing between treatment & enhancement is probably illusory
- Regulatory posture toward novel biotechnologies is in flux
- Promoting responsible research is key
 - Best practices: basic science and careful clinical translation (examples: embryology, infertility, disease modeling)
- **Goal:** Ensure that (1) research focuses on knowledge production, so that (2) only well-supported interventions based on responsible research make it into the clinic

A Final Thought

“Let us not forget that progress is an optional goal, not an unconditional commitment, and that its tempo in particular, compulsive as it may become, has nothing sacred about it. Let us also remember that a slower progress in the conquest of disease would not threaten society, grievous as it is to those who have to deplore that their particular disease be not yet conquered, but that society would indeed be threatened by the erosion of those moral values whose loss, possibly caused by too ruthless a pursuit of scientific progress, would make its most dazzling triumphs not worth having.”

--Hans Jonas, “Philosophical Reflections on Human Experimentation,” 98 *Daedalus* 219, 245 (1969).